

Amendments to the Specification:

Please replace Paragraphs [[0030, 0031, 0042, 0043, 0083, 0089, 0092, 0093, 0099, 0106 0150, 0156, 0157, 0179, 0180, 0186, 0187 and 190]] with the following respectively amended paragraphs:

[0030] FIGS. 6A and 6B ~~show~~ shows a technique for testing nerve response using specially tailored laser pulse shapes.

[0031] FIGS. 7A and 7B ~~show~~ shows traces of heat sensitive neurons for various power and pulse durations.

[0042] FIG. 18 ~~show~~ shows results of drug action on C fiber stimulation in rats.

[0043] FIG. 19 ~~show~~ shows results of drug action on A-delta fiber stimulation in rats.

[0083] The above laser systems can produce laser pulses with durations of 1 ms-200 sec with an accuracy of +/-1 ms and power of 50 mW-20 W with an accuracy of +/-0.5%. The several models of controllers as well as turnkey systems that include a laser diode module, laser driver and program controller that ~~comply~~ comply with these specifications are available on the market: S20-980-1, Apollo Instruments Inc; BWF4, BWTEK office located in 825 Dawson Drive, Suite 1 Newark, Del. 19713. (OEM), as described above. The controller preferably also controls laser current and the temperature of laser diodes inside the laser module and monitors lasing power and set up power and control power and state (switch on/off) of the pilot (aiming) beam.

[0089] In FIG. 3 temperature feedback is provided with thermal infrared sensor 16 that can be used to control the temperature--time profile with a precision of less than 1 millisecond and 1 degree centigrade. In FIG. 4 a two dimensional scanner 16 is used to provide a precise illuminated pattern on a target area 20. Scanners such as Model SCANcube.RTM. 7 (available from SCANLAB AG with offices in Cincinnati, Ohio) ~~provides~~ provide scans with a precision of about 5 mrad. In FIG. 5 a single laser (that

could provide either 980-nm pulses or 1450-nm pulses) is used to illuminate two regions at the same time or with tunable time delay. In another embodiment a single controller controls two completely separate laser systems each with its own laser driver. This could be important in experiments when measuring response times to separate pain events.

[0092] FIG. 9[[,]] shows results of ion-channel experiments performed by Applicant with the above-identified 980-nm laser system. The laser heat induced current of inside-out membrane patches from VR1-expressed HEK293 cells. The cells were stimulated by laser light and electro-physiological responses were recorded using a standard patch-clamp protocol. The laser stimulus evoked TRPV1-mediated currents based on their characteristic current-voltage profile and the absence of such responses in cells not expressing VR1. A trace of the response is provided in FIG. 9. The size of membrane patches was around 10 microns, pulse duration 100 ms, and the size of irradiated area 100 microns.

[0093] It is well known that for heat induced simulation of prick-pain stimulation the temperature of the skin has to be more than 46-48 C degree and the ramp of heating has to be over 70-100 C ~~degree~~ degrees per second. However, these data were based on pulse durations of more than 300 ms. To the best of Applicant's knowledge, there are not any data in the literature relating absolute temperature and ramp of heating for stimuli duration less than 300 ms. The best, simplest protocol, to access A-delta nociceptors and evoked monomodal pin prick pain is the following:

[0099] ~~The~~ An example of practical realization of the combination of pulse duration, beam size and pulse power for threshold pin prick pain stimulation is shown in Table 1:

[0106] 6) For determining the number of pulses that evokes threshold of pin-prick type pain; [[a]] square waved pulses within a range of pulse duration of 10-300 ms and interstimulus delay of 0.1-3 sec are applied. Examples of repetitive pulse application for A delta stimulation are shown in FIGS. 12 and 13.

[0150] Step 1: To test duration of pulse that evoked threshold warmth sensation only, the output power was set to 1.5 W, beam size adjusted to 5 mm. The pulse was applied to the skin. When the volunteer reported warmth (pain) sensation the lasing was stopped. The measured threshold pulse durations accordingly were 1300 ms for hot pain for the healthy volunteer, 800 ms hot pain for the healthy volunteer affected topical capsaicin (capsaicin decreases the thresholds of warmth sensation and hot/burning pain) and 910 ms hot pain thresholds for the volunteer with the hypersensitivity. The pulse duration for tolerance for hot pain was 2000 ms. Other studies ~~has~~ have shown that redness (skin irritation) only occurs when pulse is extended to 3000 ms.

[0156] The free 100/125 microns tip of the optical fiber of laser stimulator with an output power of 5 W was used. The distance between membrane patches fixed on pipette and tip of optical fiber was 50 microns. Three pulse powers were applied: 3 W, 4 W, 5 W. Each power set was applied with inter stimulus delay of 10 sec and a pulse duration of 50 ms. The ~~two~~ sets of two different membrane patches were provided. The results are shown in FIGS. 17A and 17B. The standard deviation of laser induced amplitude of ion channel current was less than 12% for each set of output power. There was not observed any post activation effects. The effective peak temperature of activation was determined by the following procedure: A part of membrane patches were heated until a maximum ion channel current was achieved and this procedure was repeated. At room temperature membrane patches were activated by capsaicin. The laser stimulation was used to control when (and what percentage .about.100%) ion channels are opened. Laser induced ion current decreased and DC current increase until the laser induced current decreased to 0. For kinetic protocols pulse durations from 20 to 50 msec with 4 W out put power were applied.

[0157] ~~The stimulation~~ Stimulation of C and A-delta terminals is a result of activation of heat sensitive ion channels and depolarization on cell membranes of the terminals. The research in this direction may ~~determined~~ determine what vanilloid receptors (VR1 or VRL1) are responsive for heat activation of C and A delta fibers. These receptors have different threshold temperatures and could be correspondingly linked to C or A-delta

terminals. The monitoring of their thresholds and kinetics permits the diagnosing of peripheral pain syndromes and evaluation of analgesic drug action on C and A delta terminals.

[0179] Six rats were tested with each drug. Results of ~~behavioural~~ behavioral test of rats of A delta fibers stimulation for each drug are shown in FIG. 19.

[0180] This idea was experimentally tested when the adequate laser heat stimuli were applied in vivo to the skin of volunteer and in vitro using of the somata of dorsal root ganglion (DRG) neurons. (~~Prototype paper~~). The absorption of human and animal skin of near infrared light in the interval of 900-1600 nm is mostly determined by water absorption. Thus, the location of investigated cells from DRG as well as cell membrane patches in water solution in depth close to the depths location of nociceptor terminals in the skin .about.300-600 microns can allow directly experimental comparison of activation by the same stimulation parameters of laser stimuli in vitro and in vivo.

[0186] 2) Arbitrary shape laser pulse built from 100 elements. Each element has a duration and initial and final current ~~Arbitrary shape~~ arbitrary shaped pulse that could be single ~~or~~ or repeatable (see FIGS. 10, 11, 13, 14, 15).

[0187] 3) Each arbitrary and standard pulses regimes have Trigger In and Trigger Out synchronic pulses with tunable delay. For manual access to the device Trigger In option switch off for access via PC switch on. Trigger ~~IN~~ In and Out input and output have separate BNC connectors on back side of the device

[0190] 6) Control Voltage on ~~input~~ Input Pulse Length Timer Stop